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Clinical Potential of Biological Response Modifiers Combined with Chemotherapy for Gastric Cancer

Japanese Experience

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Gastric cancer · Biological response modifiers · Cancer immunology · Chemotherapy · Chemoimmunotherapy · Immune suppression

Abstract
The most effective treatment for gastric cancer is complete surgical resection with lymphadenectomy. However, a number of patients experience recurrence of the cancer even after curative surgery. This review focuses on comparative trials studying the use of adjuvant therapy with chemotherapy plus immunotherapy in the treatment of patients with curatively resected gastric cancer. Preoperative and intraperitoneal therapy, and therapy for advanced or recurrent gastric cancer are also discussed. At present, some subset analyses of adjuvant trials have shown favorable results suggesting that the biological response modifiers (BRMs), PSK or OK-432, add a benefit to chemotherapy. For advanced gastric cancer, although gastric cancer cells are generally not very sensitive to most of the currently available chemotherapeutic agents, it has been reported that biochemical modulation with treatments including low-dose cisplatin + 5-FU (fluorouracil) have high response rates and exert an immunomodulatory effect especially when used in combination with BRMs. The impact of splenectomy and some of the promising newly developed drugs are discussed.

Introduction

Gastric cancer is one of the common cancers in the world and the most common cancer in some countries including Japan. Despite the decline in the incidence and mortality of this disease in developed countries, gastric cancer remains an important clinical issue. The most effective treatment for gastric cancer is surgical resection of the tumor with extended lymphadenectomy, which is the standard procedure in Japan. The results of this treatment depend upon the radicality of surgery, clinical staging, biological characteristics of the cancer cells and patients' immune status. Although the therapeutic results are still variable worldwide [1–5], recent statistics show a gradual improvement in the 5-year survival rate for patients with advanced gastric cancer [3]. However, some patients who have undergone curative surgery experience a relapse.

Gastric cancer cells generally do not have a high sensitivity to chemotherapy and a low immunogenicity related to stimulation of immune-competent cells. However, there is some evidence that an effective chemotherapy regimen including some biochemical modulation after resection may lead to complete eradication of the disease [6–8]. In addition, nonspecific immunopotentiation with biological response modifiers (BRMs) may enable augmentation of the host immune system, resulting in improvement of survival after surgery. In this paper, we

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review the current status of immunochemotherapy for gastric cancer and examine its clinical benefit for survival.

Immunological Background of Patients with Gastric Cancer and the Influence of Splenectomy

Many reports have been published on the immune-suppressed status of patients with cancer [9, 10]. These conditions of immune suppression are seen markedly in patients with advanced cancer. They are also often observed after the stress that is generally associated with surgery, and may be extremely strong after surgery for the treatment of malignant diseases including gastric cancer, since in these cases immune suppression is already present before surgery [11]. The mechanisms underlying these conditions are not fully understood. A lack of T-helper cell (Th)1 and Th2 is understood to be one of the possible causes, and many immune-suppressing soluble factors, including immunosuppressive acidic protein (IAP), have been reported to be increased in the serum of patients with cancer [12–14]. This is why immune activation by BRMs may be necessary after surgery for malignant diseases.

It also appears to be necessary for patients to undergo chemotherapy after gastrectomy, because a number of the patients who have been subjected to radical surgery for gastric cancer subsequently relapse and die. However, most of chemotherapeutic agents are immune-suppressive. Splenectomy is commonly performed as part of the radical surgical management of gastric cancer in the upper or entire stomach because of the potential for metastasis to the splenic hilar nodes [15, 16]. Recently, however, an insight into the role played by the spleen in the immunological defence mechanism has raised several important questions about the performance of splenectomy in these cases [17–19]. Saji et al. reported that splenectomy improves the prognosis in patients with high levels of IAP, but that preservation of the spleen and immunochemotherapy gave a significant benefit to survival in patients with low IAP levels [20]. IAP has been reported to be closely correlated with impairment of host immune response and, as mentioned here, is one of the factors that can be used to predict the effectiveness of immunotherapy [12, 13].

Immunochemotherapy as an Adjuvant Therapy for Surgery

Adjuvant chemotherapy for gastric cancer has been conducted in clinical trials since the 1950s. Since the cell-mediated immune reaction of the cancer-bearing host is suppressed, especially after surgery, immune modulators have been used to improve patients' prognosis after surgery. BRMs including polysaccharide-K (PSK), a preparation of *Streptococcus* (OK-432), polysaccharide, an extract from the culture broth of *Schizofillum commune* Fries (Sizofiran), and an extract of *Streptomyces* (Bestatin) have been developed. Among these BRMs, only PSK and OK-432 have been used for gastric cancer and their prognostic benefit when administered in combination with chemotherapy has been tested in randomized control trials. As shown in table 1, these drugs have been mainly used as a part of postoperative adjuvant therapy in a combination of chemotherapy including mitomycin (MMC), tegafur or UFT, which is a combination of tegafur and uracil in a molar ratio of 1:4 [21–32].

PSK is a protein-bound polysaccharide (beta-D-glucan) that is extracted from mycelia of the Basidiomycetes *Coriolus versicolor*, and has immunopotentiating activity. It is able to restore cancer-related immunosuppression by competing with soluble immunosuppressive factors, and to induce the production of cytokines including IL-1, IL-6, IL-8, IL-12 and tumor necrosis factor [33, 34]. It was recently also reported that PSK may bind and decrease the action of transforming growth factor beta, which is one of the major immunosuppressing soluble factors [35]. Nakazato et al. have assessed [21] the efficacy of PSK in addition to standard chemotherapy of MMC and 5-fluorouracil (FU) in patients who have undergone curative gastrectomy in a randomized controlled trial by the Study Group for Immunotherapy with PSK. Two hundred sixty-two patients were randomly assigned to MMC + 5-FU + PSK. In both arms, MMC was also given at a dose of 6 mg/m^2 postoperatively on days 0 and 1, 5-FU (150 mg PO) was administered for 4 weeks alternating with 4 weeks of rest in the control arm or with PSK (3 mg PO) in the experimental arm and continued for 10 courses. The results was that PSK improved both the 5-year disease free rate (70.7 vs. 59.4%, $p = 0.047$) and the 5-year survival rate (73.0 vs. 60.0%, $p = 0.044$). The major toxicities, such as mild myelosuppression and impairment of liver function, were equally distributed between two groups and no toxicity was identified for PSK. Sakamoto et al. have re-analyzed the results of the same trial using an interval-censored approach and confirmed the efficacy of PSK [12].

Table 1. Intra- and postoperative adjuvant immunochemotherapy for gastric cancer using BRMs

Year	Reference	Subjects number	Immunotherapy	Chemotherapy	Results
1994	Nakazato et al. [21]	Curative resection/253	PSK	MMC, 5-FU	PSK 73.0% vs. control 60.0%, $p < 0.044$
1994	Sugimachi et al. [22]	Peritoneal dissemination (synchronous)/109	OK-432 (ip)	MMC, UFT	OK-432 13.3% vs. control 11.7% (3-year survival, no difference)
1994	Maehara et al. [23]	Curative resection with serosal invasion/36	OK-432	MMC, UFT	OK-432 66.1% vs. control 26.9% (5-year survival, $p = 0.029$)
1994	Tanaka et al. [24]	Curative resection/395	OK-432 (preoperative, intratumoral)	MMC, tegafur	Overall: no difference, stage III, $p = 0.0229$
1992	Kim et al. [26]	Stage II/138, stage III/330	OK-432	MMC, 5-FU	Stage II: OK-432 44.6% vs. control 23.4% (5-year survival); stage III: OK-432 45.3% vs. control 29.8 (5-year-survival)
1992	Arinaga et al. [27]	Stage III/41	OK-432	MMC, tegafur	OK-432 67.1% vs. control 38.5% (5-year survival, $p < 0.01$)
1991	Fujimoto et al. [28]	Curative resection/264	Sizofiran	MMC, tegafur	Sizofiran 72.2% vs. control 61.9% (5-year survival, $p = 0.0731$)
1990	Niimoto et al. [29]	Serosal invasion/53, stage III + IV/53	Bestatin	MMC, tegafur	Serosal invasion: Bestatin 48.3% vs. control 13.3% (7-year survival, $p = 0.0399$); III + IV: Bestatin 48.2% vs. control 18.5% (7-year survival, $p = 0.0275$)
1990	Hattori et al. [30]	Allover/7,637	PSK, OK-432	MMC, tegafur	Insignificantly high 3-year survival rate
1989	Kondou et al. [31]	Curative resection/176	PSK	tegafur	PSK 56.5% vs. control 43.6%, $p = 0.071$ (–), ps (+), SI + S2
1986	Mitomi and Ogoshi [32]	stage II, III, IV	PSK	MMC, tegafur	PSK 60.3% vs. control 45.5%, $p = 0.005$, stage III, IV well
1981	Niimoto et al. [33]	Curative resection except M, N0/579	PSK	MMC, tegafur	4-year survival 73.2%, $p = 0.05$, ps (–), n (+), well, PPD (+)

MMC = mitomycin C; 5-FU = 5-fluorouracil; PSK = polysaccharide-K; UFT = tegafur-uracil; OK-432 = picibanil; PPD = purified protein derivative (tuberculin) (+); patients with skin reaction to PPD with redness > 10 mm in diameter; IAP = immunosuppressive acidic protein; ps = prognostic serosal invasion; ps (–) = invasion more superficial than subserosal layer of the stomach; ps (+) = invasion beyond serosal surface; n = nodal involvement by microscopic diagnosis.

OK-432 is a lyophilized, heat-inactivated, penicillin-treated preparation of a low virulence strain (Su) of *Streptococcus pyogenes* of human origin, that has been shown to stimulate natural killer cells and macrophages and enhance the production of interferon [36, 37]. Kim et al. have performed clinical trials using OK-432, MMC and 5-FU in patients with stage III gastric cancer. They found that the 5-year survival rate of surgery alone, surgery followed by chemotherapy with 5-FU and MMC, and surgery followed by immunochemotherapy with 5-FU, MMC and OK-432 was 24.4, 29.8 and 45.3%, respectively [26]. Tanaka et al. [24] described the results of the Okayama cooperative group trial comparing MMC + tegafur + OK-432 (subcutaneously administered) with or without preoperative intratumoral (it) Ok-432 treatment. Three hundred ninety-five patients were enrolled in this study between 1985 and 1986 and allocated to either the group with or without OK-432. In the experimental group, 10 KE OK-432 (1 KE: 0.1 mg dried cocci)/5 ml of saline was injected endoscopically into 5 to 10 points around the tumor 7 to 14 days before the surgery. MMC (0.4 mg/kg) was given immediately after the surgery, tegafur and OK-432 (SC) were administered from day 14 to 1 year. Toxicities of preoperative OK-432 (it) involved fever (25.5%), anorexia (22.8%), abdominal pain (15.2%), and nausea/vomiting (6.9%), and those induced by postoperative chemoimmunotherapy were similar in incidence in both groups. The 5-year survival rates were 61.5% for the OK-432 (it) group and 59.1% for the control group. Subset analysis revealed that 5-year survival rates were significantly improved by treatment with OK-432 (it) in stage III patients and in patients with nodal involve-

ment. 5 year survival rates for the 63 patients who underwent curative resection and had moderate to marked tumor-infiltrating lymphocytes (TIL) were 81% in the OK-432 (it) group and 61% in the control group ($p = 0.0407$) [24]. Gouchi et al. reported the results of this clinical trial with re-analysis after a follow-up of 10 years [25]. 10-year survival rates of the patients with nodal involvement (N2) and stage IIIa (Criteria of Japanese Gastric Cancer Society) were significantly higher in OK-432 (it) patients than in control patients (32.9 vs. 20.6% for N2 patients, 33.0 vs. 20.0% for stage IIIa patients, respectively).

Peritoneal dissemination is a predominant route of metastasis from a gastric cancer and when present, it significantly worsens the prognosis. When free cancer cells are detected in the peritoneal cavity of patients with serosal invasion, microscopic peritoneal metastases will have already been established at the time of curative surgery [39, 40]. Maehara et al. reported that the concomitant intraperitoneal administration of OK-432, MMC and UFT significantly decreased the rates of peritoneal recurrence and lengthened survival time [23]. Frasci et al. have tested intraperitoneal adjuvant combination treatment including cisplatin or carboplatin, etoposide and interferon-alpha in patients with resected gastric cancer with serosal involvement, and reported that the 5-year survival rate was significantly higher in the patients who received this particular combination treatment [41].

The direct action of BRMs, especially cytokines such as interferon and tumor necrosis factor on tumor cells is well known. Interferon and tumor necrosis factor can exert cytostatic and cytotoxic effects on tumor cells. However, there are only a few reports on the direct cytotoxic or cytostatic action of classical BRMs such as OK-432 [42, 43]. The immunomodulating effect of PSK is considered to be derived from its activity on immunocompetent cells. However, recently, PSK was shown to possess (1) inhibitory effect on proliferation of tumor cells; (2) cytostatic effect on the invasion of tumor cells, and (3) modulatory effect on the expression of surface molecules on tumor cells as HLA. Although the major action of these two classical BRMs developed in Japan is host-mediated immunoregulation, their direct effects to the tumor cells seem to be very important as a mechanism for antitumor activity.

Chemotherapy for Advanced Gastric Cancer and the Immuno-Modulating Action of Low-Dose Chemotherapy

Even after the curative resection of gastric cancer with regional lymph node dissection, recurrence may be frequent. For patients with unresectable recurrent foci, the remaining treatment choices are chemotherapy or immunochemotherapy. Recently, a new concept of biological modulation has been developed and there are many protocols used not only for gastric cancer, but also for other malignant diseases. For a decade, clinical trials of combination of protocols of three or more chemotherapeutic agents for gastric cancer such as EFP (etoposide, 5-FU and cisplatin), ELF (leucovorin, etoposide, 5-FU) or FLEP (5-FU, leucovorin, etoposide and cisplatin) have been carried out for gastric cancer [44–46]. From the view point of immunochemotherapy or immunomodulatory effects of chemotherapy, it has been reported that biochemical modulation of 5-FU or low-dose chemotherapy might modulate the host-cell-mediated immune reaction, that this action might be more effective in combination with BRMs such as PSK or lentinan which is purified beta-glucan obtained from *Lentinus edodes* [47], and that it can alter the immunological background of patients with far advanced cancer [48–51]. This evidence has, in part, led to the use of low-dose cisplatin + 5-FU for a variety of human malignancies including gastric cancer in Japan. Ishikawa reported that low-dose CDDP-5-FU prevented the suppression of postoperative NK activity, while the bolus administration of MMC impaired the recovery of the depressed NK cell activity [52]. A newly developed oral anticancer drug, S-1, which is composed of tegafur, gimestat and otastat potassium in a molar ratio of 1:0.4:1 now used for gastric cancer. This biochemical modulation of a 5-FU-based compound has shown a high response rate (49%) in patients with advanced gastric cancer [53]. Clinical trials of S-1 with cisplatin or leucovorin are now been performed, and the results concerning its immune-modulation effects when administered in a combination with BRMs are awaited with much interest.

Conclusions

Surgical complete resection with regional lymph node dissection and the management of patients with gastric cancer have been already developed and in use. However, a number of the patients who undergo curative resection suffer a recurrence, and over the years, many different

ways of treating these patients have been tested. Many random assignment trials have reported that there are no confirmed western trials in which adjuvant therapy has clearly increased the cure rate in resectable gastric cancers. Until now, although most Japanese randomized adjuvant trials for curatively resected gastric cancer have failed to show a definite survival advantage, subset analyses often clearly show many favorable results for those patients who have received pathologically curative resection. To date, to our knowledge, adjuvant chemoimmunotherapy after surgery is not necessary for patients with early stages (with only mucosal and submucosal invasion). PSK can be used for advanced patients because it may modify an immune-suppression that appears in these patients, while other BRMs such as OK-432 may also induce immune-suppressing cytokines including IL-10 or transforming growth factor. As a chemotherapeutic agent that may be combined with BRMs, S-1 may be promising and the results of the clinical trials of the protocols containing S-1 and BRM are awaited with much interests.

For patients with advanced or recurrent gastric cancer, it is not only important to have a high response rate, but also longer survival. It has also been shown that the effects of chemotherapy found in tumor-shrinkage does not correlate with the better survival of the patients, and that some with advanced gastric cancer who have been treated with biochemical modulation and BRMs have survived for longer and with a fair quality of life without any decrease in the size of their tumor mass. We must now look at these cases and consider new criteria, with which we can judge precisely how they have responded. Recent advances in molecular biology may expand our options for immunochemotherapy in treating gastric cancer.

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